Transforming growth factor-beta activation promotes genetic context-dependent invasion of immortalized melanocytes.

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Public Summary:

Scientific Abstract:
Accumulation of distinct sets of genetic/epigenetic alterations is thought to contribute to stepwise progression of human cutaneous melanomas. We found evidence of frequent tumor cell autonomous transforming growth factor-beta (TGF-beta) signal activation in both premalignant and malignant stages of human cutaneous melanoma histogenesis and investigated its potential causative roles using human organotypic skin cultures. PTEN deficiency and Braf activation, two common coincident genetic alterations found in primary cutaneous melanomas, were first introduced into human melanocytes previously immortalized by the SV40 large T antigen and telomerase. These changes individually supported anchorage-independent growth and conferred benign, hyperplastic growth in a skin-like environment. In addition, PTEN deficiency combined with Braf activation together induced a melanoma in situ-like phenotype without dermal invasion. Further addition of cell autonomous TGF-beta activation in the context of PTEN deficiency and Braf activation promoted dermal invasion in skin cultures without significantly promoting proliferation in vitro and in vivo. This proinvasive phenotype of cell autonomous TGF-beta activation is genetic context-dependent, as hyperactivating the TGF-beta type I receptor without PTEN deficiency and Braf activation failed to induce an invasive behavior. Evidence of genetic interactions among PTEN deficiency, Braf activation, and cell autonomous TGF-beta activation shows that distinct stages of human melanoma are genetically tractable in the proper tissue architecture.